--48. A replicable expression vehicle comprising the DNA molecule of claim ~~46~~ 47 and capable, in a transformant host cell, of expressing said protein.

--49. A host cell selected from the group consisting of a prokaryotic and a eukaryotic cell transformed with the replicable expression vehicle of claim ~~47~~ 48.

--50. A process for producing a protein having the amino acid sequence of an active fragment of TBP-II, comprising the steps of: (a) culturing a transformant host cell according to claim ~~48~~ 49 in a suitable culture medium, and (b) isolating said protein.--

REMARKS

Claims 11-14 and 34-50 presently appear in this case. No claims have been allowed. Claims 14, 39, 42 and 45 have been withdrawn from consideration although the examiner has indicated that, in the event that the claims currently under consideration are found allowable, the withdrawn claims would be treated as per MPEP §821.04. The Advisory Action of December 2, 1997, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

In accordance with 37 C.F.R. §1.129(a), applicants hereby request that the finality of the official action of July 2, 1997, be withdrawn. The check attached hereto includes payment of the $790.00 fee required by 37 C.F.R. §1.129(a) and §1.17(r). The present application clearly falls within the transitional provisions of 37 C.F.R. §1.129(a) as it claims the

benefit of the effective filing date of U.S. application no. 07/524,263, filed May 16, 1990, which is more than two years prior to June 8, 1995.

Note that 37 C.F.R. §1.129(a) states:

> The finality of the final rejection is automatically withdrawn upon the timely filing of the submission and payment of the fee set forth in §1.17(r).

It is hereby requested that applicants' supplemental amendment of March 31, 1998, as well as the present amendment, be entered and considered in light of the withdrawal of the finality of the previous rejection. It is further requested that applicants' amendment of November 3, 1997, in conjunction with applicants' supplemental amendment of March 31, 1998, and the present second supplemental amendment, be considered to be the submission responsive to the official action of July 2, 1997. As the fee required by §1.17(r) is being paid herewith, all requirements of 37 C.F.R. §1.129(a) have now been met. Withdrawal of the finality of the official action of July 2, 1997, is therefore respectfully urged.

In the advisory action of December 2, 1997, claims 35 and 36 were rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors at the time the invention was filed had possession of the claimed invention for the reasons elaborated in the previous office action. This rejection is respectfully traversed.

The examiner's attention is respectfully invited to applicants' supplemental amendment of March 31, 1998. In this amendment, claims 35 and 36 were amended in a manner which obviates this rejection for the reasons set forth in the remarks accompanying that supplemental amendment. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Claims 11-13, 33-38, 40, 41, 43 and 44 have been rejected under 35 USC 102(e) as anticipated by Smith. This rejection is respectfully traversed.

The examiner's attention is again invited to applicants' supplemental amendment of March 31, 1998. The amendment to claims 11, 35 and 36 as set forth in that amendment render the claims entitled to the effective filing date of the priority document Israel 90,339, thus antedating this reference. The additional changes to claim 11 presented herein are being made in order to help to obviate the 35 USC 112 rejection. However, the additional subject matter finds full support in the 90,339 application in sections 2.2-2.4 at pages 12-14 thereof. Accordingly, newly amended claim 11 is entitled to the effective filing date of Israel application 90,339 for the same reason that claim 11 was entitled to this date prior to the present amendment, i.e, the reasons discussed in the supplemental amendment of March 31, 1998.

New claims 46-50 are also entitled to the effective filing date of the Israel application 90,339. Note the paragraph bridging pages 9 and 10, where it states:

> As "active fractions" of the substantially purified protein, the present invention covers any fragment or precursors of the

> polypeptide chain of the protein molecule alone ... provided said fraction has the ability to inhibit the cytotoxic effect of TNF on cells.

A similar statement appears in the present specification in the second paragraph of page 15.

As all of the present claims are entitled to the effective filing date of Israel application 90,339, Smith is not available as a reference against any of the present claims. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Claims 11-13, 33-38, 40, 41, 43 and 44 have been rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains or with which it is most nearly connected to make and/or use the invention. The examiner states that there is no disclosure of the complete sequence of any protein nor is there any disclosure of even a single nucleic acid sequence that would meet the limitations of the claims. The examiner states that there is inherent unpredictability in making nucleic acids to encode proteins which are defined almost solely by function. The examiner states that there is no disclosure in the specification as to whether the particular amino acid sequences listed on page 23 are derived from the same molecule or that the molecule is found as four different but related molecules. The examiner states that there is no guidance in the specification as to whether the four potential forms of TBP-II are

functionally active or the nature of the identity of the functionally active molecule. The examiner states that the claims encompass DNAs encoding TBP-II binding protein regardless of whether said proteins do or do not have the other characteristics disclosed in the specification for TBP-II binding protein, e.g., a particular molecular weight or reactivity with polyclonal antibodies prepared against whole purified TBP-II as disclosed in example 3 of the specification. Thus, the examiner states that the claims potentially encompass DNA encoding TBP-II that is not disclosed in the specification. The examiner states that it is unclear whether the claimed DNA encodes one protein or several related proteins of differing amino acid lengths with different N-terminal sequences. The examiner states that the specification at page 7, lines 10-11, does not indicate whether the heterogeneitiy is related to different variants of TBP-II binding protein or longer or shorter versions of the same molecule. Thus, the examiner does not consider the claimed DNA to encode one protein. The examiner relies on In re Deuel for the proposition that disclosure of a partial protein sequence does not render obvious the DNA encoding that sequence. This rejection is respectfully traversed.

Applicants would very much like to dispose of the issue that the claims encode proteins which are defined solely by function. The present examples in the present specification show exactly how the presently claimed protein was separated from urine. After affinity purification on a column of

immobilized TNF, TBP-I was separated from TBP-II by reversed phase high pressure liquid chromatography. As shown in Figure 1 and disclosed at page 21 in the paragraph below the table, the active proteins were found to elute from the HPLC column as two distinct protein peaks, in fractions corresponding to about 27% acetonitrile (TBP-I) and about 31% acetonitrile (TBP-II). The TBP-II fraction was then subjected to SDS-PAGE as shown in Section 1.4 beginning at page 22. The results are shown in Figure 2B in which the protein appears at a molecular weight of about 30 kDa. It is that substantially purified TBP-II which was subjected to N-terminal sequence analysis in Section 1.5 beginning at page 23 of the specification. Samples were subjected to repetitive cycles of Edman degradation in an automated pulsed liquid gas phase protein microsequencer. Three separate analyses were performed in order to confirm the sequence data. The initial yield was over 40% indicating that the major protein in the preparation (the 30 kDa band) is related to the resulting sequence.

All of this shows that the protein of fractions 27 and 28 have a common portion of the N-terminal sequence, with some shorter by 3 to 5 amino acids than the others. As all of these are in the 30 kDa band, it is not understood why the examiner takes the position that one of ordinary skill in the art reading the present specification may believe that the different heterogeneities may be completely different sequences of substantially different length having only a coincidental sequence identity of at least 10 amino acids in the N-terminal

region. The fact that they all elute into biologically active fractions by HPLC under conditions which separate the TBP-II proteins from the TBP-I proteins and the fact that the proteins of the entire active fraction show a single molecular weight band on SDS-PAGE, would lead one of ordinary skill in the art to understand that the N-terminal heterogeneities described in the specification are just that, heterogeneities at the N-terminus of a single TBP-II protein, such heterogeneities being so minor that they are not separated into different molecular weight bands upon SDS-PAGE. Furthermore, the fact that fractions 27 and 28 both have substantial biological activity even though one is predominantly the Phe-Thr-Pro truncation, while the other is predominantly the Val-Ala-Phe-Thr-Pro molecule, would suggest that all of these truncations are biologically active. Certainly, one would not expect that a truncation of three amino acids at the N-terminus of a 30 kDa protein would destroy the activity of that protein.

Accordingly, it is urged that claim 35 is directed to a single fully disclosed protein which may have minor N-terminal heterogeneities. In order for the examiner to further assure himself that applicants are not catching other non-disclosed molecules by the definition of claim 35, the examiner is invited to do a sequence search for what is known today about the disclosed sequence. It can be seen that even today, nine years after the effective filing date of the present invention, what is commonly known as TBP-II is the only naturally occurring protein which has this partial sequence, and certainly the only

one with that sequence which has the ability to inhibit the cytotoxic effect of TNF.

In a further attempt to obviate this rejection, claim 11 has been amended to further identify the protein in a manner fully supported by the present application and by the priority application so as to make it even further clear that the claims only cover DNA encoding a single protein which may have a heterogeneity at the N-terminus. Claim 11 now specifies that the naturally occurring TBP-II protein is one which, after being purified by affinity chromatography with TNF-α, elutes from a reversed phase high pressure liquid chromatography column in a fraction corresponding to about 31% acetonitrile and shows an apparent molecular weight of about 30 kDa when measured by reducing SDS-PAGE. As this claim contains the other characteristics disclosed in the specification for TBP-II proteins, the examiner's objection about the claim encompassing DNAs encoding TBP-II regardless of whether the proteins do or do not have the other characteristics disclosed in the specification, has been obviated. Claim 11 inserts the other characterizing data from the specification so as to further define the protein. Thus, it is urged that at least with respect to claim 11 and also with respect to claim 36, which already recites a molecular weight, as well as claim 35 for the reasons discussed hereinabove, the claims are no longer subjected to the type of rejection about which the examiner relies upon Ex parte Maizel, 27 USPQ2d 1662, as the claims do not read on all "biologically functional equivalents". Indeed,

these claims do not read on any biologically functional equivalent but only on the protein described in the specification, which protein may have a minor amount of N-terminal heterogeneity.

Once it is established that the protein encoded by the DNA of the claims is a single protein sufficiently defined so as to fingerprint it and distinguish it from all other known proteins, then the only remaining issue is whether the holding of the Federal Circuit in In re Deuel requires rejection of the DNA claims based on the written description requirement of the first paragraph of 35 USC 112. In this regard, the examiner's attention is again invited to the detailed discussion of this issue in applicants' amendment of November 3, 1997. The examiner's discussion of the issues raised by applicants in that amendment, as set forth in the Advisory Action, were obscured by the examiner's position that the claims did not define the protein encoded by the DNA in such a manner as to encompass only the disclosed TBP-II. Once it is established that the present claims, or at least claims 11 and 36, adequately fingerprint the disclosed TBP-II protein, then the only issue is whether it would be within the skill of those of ordinary skill in the art to complete the sequencing of this protein. If so, once someone has the complete amino acid sequence of the protein, one automatically has all the DNA sequences which encode that protein. The present claims are not directed to the naturally occurring DNA gene encoding this protein, but the present claims are generic to all DNA sequences which encode the protein. As

stated in In re Deuel, claims which generically encompass all DNA sequences encoding a protein in question would have been obvious from the complete amino acid sequence of the protein coupled with the knowledge of the genetic code (34 USPQ2d at 1216).

Since the TBP-II protein has been adequately conceived and described (note that claims to this protein have been allowed in the parent case) and this protein is adequately defined in the present claims for the reasons discussed above, the sequence is inherent and can be determined without undue experimentation. Once one is in possession of the sequence of the protein, the generic DNA claims are adequately described in light of the genetic code. Accordingly, reconsideration and withdrawal of this rejection are also respectfully urged.

New claims 46-50 have now been added which are identical to claim 11 but which further specify that the isolated DNA molecule may comprise the nucleotide sequence coding for a fragment of said TBP-II which has the ability to inhibit the cytotoxic effect of TNF. Assuming that claim 11 is allowable for the reasons discussed hereinabove, claim 46 should be allowable for the same reasons, as the fragments are adequately disclosed in the present specification and in the priority application (as discussed above) and it would not involve undue experimentation to determine the identity of all fragments of TBP-II which have the ability to inhibit the cytotoxic effect of TNF. Paragraph 15, page 2, of the present specification discloses that the present invention covers any

fragment of TBP-II which has the ability to inhibit the cytotoxic effect of TNF on cells. It would not involve undue experimentation, once one of ordinary skill in the art was in possession of the TBP-II protein, to remove amino acids one at a time from either end of the protein and test each resultant in the simple bioactivity test disclosed in the present specification (see the first full paragraph at page 20 of the present specification). Claim 46 does not encompass changing of amino acids but only deleting amino acids from the ends (not the middle) and then determining whether the resultant fragment is active. This is well within the skill of those of ordinary skill in the art and would not involve undue experimentation. Accordingly, applicants are entitled to claim DNA encoding such active fragments. Thus, claims 46-50 are also allowable for the same reasons as discussed above with respect to claim 11.

It is submitted that all of the claims now present in the case clearly define over the references of record and fully comply with 35 USC 112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

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